General

Guideline Title

Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ.

Bibliographic Source(s)

Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, Horton J, Hwang S, Johnson PL, Marinovich ML, Schnitt SJ, Wapnir I, Moran MS. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. J Clin Oncol. 2016 Nov 20;34(33):4040-46. [36 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the strength of recommendation (Strong, Moderate, Weak) and strength of evidence (Strong, Moderate, Weak) are provided at the end of the "Major Recommendations" field.

Clinical Question

Are positive margins associated with an increased risk of ipsilateral breast tumor recurrence (IBTR)? Can the use of whole-breast radiation therapy (WBRT) mitigate this increased risk?

Recommendation: A positive margin, defined as ink on ductal carcinoma in situ (DCIS), is associated with a significant increase in IBTR; this increased risk is not nullified by the use of WBRT. (Strength of Recommendation: Strong; Level of Evidence: Meta-analysis [patient level] of randomized controlled trials [RCTs] [not primary endpoint]; meta-analysis [study level] of observational studies; individual RCT; Strength of Evidence: Strong)

Clinical Question

What margin width minimizes the risk of IBTR in patients receiving WBRT?

Recommendations

a. Margins of at least 2 mm are associated with a reduced risk of IBTR relative to narrower negative margin widths in patients receiving WBRT. (Strength of Recommendation: Moderate; Level of Evidence: Meta-analysis [study level] of observational studies; Strength of Evidence: Moderate)
b. The routine practice of obtaining negative margin widths wider than 2 mm is not supported by the evidence. (Strength of Recommendation: Strong; Level of Evidence: Meta-analysis [study level] of observational studies; Strength of Evidence: Strong)

Clinical Question

Is treatment with excision alone and widely clear margins equivalent to treatment with excision and WBRT?

Recommendation: Treatment with excision alone, regardless of margin width, is associated with substantially higher rates of IBTR than treatment with excision and WBRT (even in predefined low-risk patients). (Strength of Recommendation: Strong; Level of Evidence: Meta-analysis [patient level] of RCTs; individual RCT; Strength of Evidence: Strong)

Clinical Question

What is the optimal margin width for patients treated with excision alone?

Recommendation: The optimal margin width for treatment with excision alone is unknown, but should be at least 2 mm. Some evidence suggests lower rates of IBTR with margin widths wider than 2 mm. (Strength of Recommendation: Moderate; Level of Evidence: Meta-analysis [study level] of observational studies; prospective single-arm studies; retrospective studies; Strength of Evidence: Moderate)

Clinical Question

What are the effects of endocrine therapy on IBTR? Is the benefit of endocrine therapy associated with negative margin width?

Recommendation: Rates of IBTR are reduced with endocrine therapy, but there is no evidence of an association between endocrine therapy and negative margin width. (Strength of Recommendation: Weak; Level of Evidence: RCTs; Strength of Evidence: Weak)

Clinical Question

Should margin widths greater than 2 mm be considered in the presence of unfavorable factors such as comedo necrosis, high grade, large size of DCIS, young patient age, negative estrogen receptor (ER) status, or high risk multigene panel scores?

Recommendation: Multiple factors have been shown to be associated with the risk of IBTR in patients treated with and without WBRT, but there are no data addressing whether margin widths should be influenced by these factors. (Strength of Recommendation: Weak; Level of Evidence: Expert opinion; Strength of Evidence: Weak)

Clinical Question

Should margin width be taken into consideration when determining WBRT delivery technique?

Recommendation: Choice of WBRT delivery technique, fractionation, and boost dose should not be dependent upon negative margin width. There is insufficient evidence to address optimal margin widths for accelerated partial breast irradiation (APBI). (Strength of Recommendation: Weak; Level of Evidence: Retrospective studies; expert opinion; Strength of Evidence: Weak)

Clinical Question

Should DCIS with microinvasion be considered as invasive carcinoma or DCIS when determining optimal margin width?

Recommendation: DCIS with microinvasion, defined as no invasive focus >1 mm in size, should be considered as DCIS when considering the optimal margin width. (Strength of Recommendation: Weak; Level of Evidence: Expert opinion; Strength of Evidence: Weak)

Definitions

The American College of Physicians' Guideline Grading System

Quality of Evidence	**Strength of Recommendation**	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	**Benefits Finely Balanced With Risks and Burden**
High	Strong	Weak
	Insufficient evidence to determine net benefits or risks	

Quality of Evidence	Strong	Strength of Recommendation	Weak
High	**Benefits Clearly Outweigh Risks and Burden**	**Benefits and Burden or Risks and Burden Clearly Outweigh Benefits**	**Benefits Finely Balanced With Risks and Burden**
Moderate			
Low			
Insufficient evidence to determine net benefits or risks			

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Ductal carcinoma in situ (DCIS)

Guideline Category

Management

Risk Assessment

Treatment

Clinical Specialty

Oncology

Radiation Oncology

Surgery

Intended Users

Patients

Physicians

Guideline Objective(s)

- To evaluate ipsilateral breast tumor recurrence (IBTR) in relation to margin width in patients with ductal carcinoma in situ (DCIS) receiving breast-conserving surgery
- To address the question "what margin width minimizes the risk of IBTR in patients with DCIS receiving breast-conserving surgery?"
- To assist treating physicians and patients in the clinical decision-making process based on the best available evidence

Target Population

Patients with ductal carcinoma in situ (DCIS) receiving breast-conserving surgery

Interventions and Practices Considered

1. Determination of optimal margin width to minimize risk of ipsilateral breast tumor recurrence (IBTR)
2. Whole-breast radiation therapy (WBRT) in combination with excision
3. Excision alone
4. Endocrine therapy
5. Consideration of unfavorable risk factors in determining margin width
6. Choice of WBRT delivery technique, fractionation, and boost dose
7. Considerations for ductal carcinoma in situ (DCIS) with microinvasion when determining optimal margin width

Major Outcomes Considered

Ipsilateral breast tumor recurrence (IBTR)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The methods are described in full in the meta-analysis companion to this guideline (see the "Availability of Companion Documents" field) and are summarized briefly below.

Study Eligibility Criteria

Eligible studies enrolled ≥50 women with ductal carcinoma in situ (DCIS) undergoing breast conserving surgery (BCS); allowed calculation of the crude local recurrence (LR) rate by microscopic margin status; defined negative margins by a numeric threshold; reported mean or median age; and presented mean or median follow up of ≥48 months.

Literature Search

MEDLINE, PREMEDLINE, EMBASE, and ALL EBM REVIEWS were searched in October 2014, for studies published from 1992 to 2015. One investigator screened citations, with a sample independently screened by a second. Details of the search strategy used are provided in the online supplementary material to the systematic review.

Number of Source Documents

The meta-analysis included 20 studies. See the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart in online supplementary Appendix C of the systematic review (see the "Availability of Companion Documents" field). All publications in the meta-analysis (except for two) were retrospective and provided observational data at the study level. The characteristics of these studies have been reported in the meta-analysis.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

The American College of Physicians' Guideline Grading System

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	**Benefits Finely Balanced With Risks and Burden**
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The methods are described in full in the meta-analysis companion to this guideline (see the "Availability of Companion Documents" field) and are summarized briefly below.

Data Extraction

Two investigators independently extracted data; disagreements were arbitrated by a third investigator.

Meta-Analysis

Analysis was performed using two different statistical approaches. In the frequentist approach, multiple margin cut points within studies, if reported, were condensed into a single cut point, while the Bayesian approach allowed for the use of multiple cut points. All reported odds ratio (ORs) were adjusted for study-specific median follow up time (to account for the inherent increased risk of ipsilateral breast tumor recurrence [IBTR] with longer follow up) and are reported relative to positive (or positive/close) margins, or to a minimal negative margin (no ink on tumor or margin >1 mm).

Statistical Analysis

Frequentist Models (Random Effects Logistic Meta-regression)

Margins were dichotomised into positive/close versus negative margin status using one distance threshold per study (>0 or 1 mm; 2 mm; 3 or 5 mm; 10 mm). The association between local recurrence (LR) and margin status and distance was modeled using random effects logistic meta-regression. ORs are presented for negative relative to positive/close margins, and threshold distances relative to >0 or 1 mm.

Bayesian Models (Network Meta-analysis)

Network meta-analysis using mixed treatment comparisons used data from single or multiple thresholds within studies (when presented) to compare directly (within study) and indirectly (between studies) the probability of LR between margins categories (positive; >0 or 1 mm; 2 mm; 3 mm; 10 mm). ORs compare negative versus positive margins, and distance categories relative to positive margins.

Assessment of Covariates

All models were adjusted for study-level follow up time. Other covariates were assessed for their effect on model estimates (age; median year of recruitment; proportion of patients who received endocrine therapy; proportion with high-grade ductal carcinoma in situ (DCIS); proportion of patients receiving whole breast radiation).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Society of Surgical Oncology (SSO), American Society for Radiation Oncology (ASTRO), and the American Society of Clinical Oncology (ASCO) convened a multidisciplinary margins panel (MP) to evaluate ipsilateral breast tumor recurrence (IBTR) in relation to margin width. The primary question addressed was "what margin width minimizes the risk of IBTR in patients with ductal carcinoma in situ (DCIS) receiving breast-conserving surgery?"

Committee members were chosen by their respective organizations based upon interest and expertise in DCIS management. Processes recommended in the Institute of Medicine report "Clinical Practice Guidelines We Can Trust" which were followed as part of the guideline development process included: (1) the development of a systematic review/study-level meta-analysis based on questions to be addressed by the MP to serve as the primary evidence base, with additional topic-specific literature reviews conducted by participants for questions not addressed in the meta-analysis; (2) the provision for each recommendation of a rating of the strength of the evidence and the strength of the recommendation; (3) the ascertainment of the level of agreement of panel members with each recommendation by vote, and the revision of recommendations to achieve greater than 90% consensus; and (4) the declaration by MP candidates of potential conflicts of interest before convening, and the obtaining of written disclosures at the consensus meeting.

The MP convened in November 2015; the resulting manuscript was approved by all panel members.

Rating Scheme for the Strength of the Recommendations

See the "Rating Scheme for the Strength of the Evidence" field.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The margins panel (MP) convened in November 2015; the resulting manuscript was approved by all panel members and externally reviewed, and feedback was incorporated. The final manuscript was approved by the Society of Surgical Oncology (SSO) Executive Council, the American Society for Radiation Oncology (ASTRO) Board of Directors, and the American Society of Clinical Oncology (ASCO) Board of Directors, and endorsed by the Board of Directors of the American Society of Breast Surgeons.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field). All publications in the meta-analysis (except for two) were retrospective and provided observational data at the study level.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The use of a 2 mm margin as the standard for an adequate margin in ductal carcinoma in situ (DCIS) treated with whole-breast radiation therapy (WBRT) is associated with low rates of ipsilateral breast tumor recurrence (IBTR) and has the potential to decrease re-excision rates, improve cosmetic outcome, and decrease health care costs.

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

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- There are limitations to this guideline. It applies to patients with ductal carcinoma in situ (DCIS) and DCIS with microinvasion (DCIS-M) treated with whole-breast radiation therapy (WBRT). The findings should not be extrapolated to DCIS patients treated with accelerated partial breast irradiation (APBI) or those with invasive carcinoma for whom a separate guideline has been developed. While studies including patients treated with and without WBRT were included in the meta-analysis, a meta-analysis of studies of treatment with excision alone was not conducted. Additionally, all of the studies included in the meta-analysis were retrospective. However, in the absence of any planned prospective randomized trials addressing the question of margin width and local recurrence, these studies represent the best available evidence for clinical decision making.

Implementation of the Guideline

Description of Implementation Strategy

For information on the American Society for Clinical Oncology (ASCO) implementation strategy, please see the ASCO Web site .

Implementation Tools

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, Horton J, Hwang S, Johnson PL, Marinovich ML, Schnitt SJ, Wapnir I, Moran MS. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. J Clin Oncol. 2016 Nov 20;34(33):4040-46. [36 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Nov 20

Guideline Developer(s)

American Society for Radiation Oncology - Professional Association

American Society of Clinical Oncology - Medical Specialty Society

Society of Surgical Oncology - Medical Specialty Society

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Guideline Committee

Expert Panel

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The Expert Panel was assembled in accordance with the American Society of Clinical Oncology's (ASCO's) Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the panel did not disclose any relationships constituting a conflict under the Policy.

Authors' Disclosures and Potential Conflicts of Interest

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc .

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Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Clinical Oncology Web site .

Availability of Companion Documents

The following are available:

- Marinovich ML, Azizi L, MacAskill P, Irwig L, Morrow M, Solin LJ, Houssami N. The association of surgical margins and local recurrence in women with ductal carcinoma in situ treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol. 2016 Nov;23(12):3811-21. Available from the Annals of Surgical Oncology Web site .
- Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2016. 12 p. Available from the American Society of Clinical Oncology (ASCO) Web site .
- Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. Summary of recommendations. Alexandria (VA): American Society of Clinical Oncology; 2016. 2 p. Available from the ASCO Web site .

Patient Resources

None available

NGC Status

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